Reviewer's report

Title: Dose patterns in subjects chronically exposed to opioids: a large cohort study in the United States

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Reviewer: Mark Edlund

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This is a nice paper, and contributes to our knowledge in an important and controversial area--the use of chronic opioids for pain, and how opioid dose may or may not escalate over time. This is a content area that I am familiar with, and I don’t recall ever seeing a paper such as this.

The following are all major compulsory revisions:

I did have two questions that need to be clarified.

(1) Just to be clear, are “strong” opioids those opioids in table 1? Or those in table 2? It must be those in table 2, as clearly buprenorphine does not meet the criteria, and it does not seem like tramadol would either.

(2) How was it known whether patients were receiving opioids for treatment of opioid addiction? That is, if a patient was on methadone, how was it known whether the methadone was for pain or addiction? However, this is a relatively minor issue, as so few were on methadone.

However, my major concern is with the set up of the study, and interpretation of the data.

(3) High utilizers of opioids tend to be a fairly small group, and by focusing on measures such as the median, mean, P25, and P75, do we adequately capture what is happening? For example, it might be interesting to see what happened in the 95th percentile.

(4) In the strictest sense, this type of analysis does not actually investigate dose escalation in individuals. Consider the simple example where there are just two individuals—each at 100 mg morphine dose. Say in the next period one individual increases his/her use to 180 mg, and the other decreases to 20 mg. In this case, with this type of analysis we would say there was no dose escalation, but really what happened was there was both dose escalation and dose reduction. Thus, the author’s analysis focuses on dose escalation in the group, but really does not get at dose escalation in individuals. Is there a way the authors could look at this? For example, I think the study would be much more informative if it looked at the percentage of individuals whose dose was 50% higher after one year, or 50% higher after two years (just an example).

(5) I think the authors are over-optimistic in how they characterize their conclusions. For example, they write in the abstract “Dose escalation is also
uncommon in the first 2 years of continuous exposure to opioids, especially in those subjects with non-malignant conditions.” However, the mean dose among all patients did increase from 63 to 78, a 24% increase, in the first two years. Further, the abstract does not mention that in those with continuous exposure, after 4 years the mean has more than doubled, as has the P75—although this is dealt with in the text. Thus, the data could be “spun” a different way. Similarly, the authors write “the low proportion of subjects who required very high doses of opioids confirmed that large dose escalation is a relatively uncommon phenomenon”. However, 7.6% of individuals of continuous opioids patients were at some point on a dose greater than 180 mg—some might characterize this as a low proportion, others might not.

In summary, the data presented are helpful, but the paper would really be strengthened by additional analyses that are more informative at the individual level.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests